REMARKS

Upon entry of the foregoing amendment, claims 14, 16-20, and 28-35 are pending in the application, with 14 and 29 being the independent claims. Claim 20 has been withdrawn by the Examiner. New claims 29-35 have been added. Support for the new claims is found throughout the specification, including *inter alia*, at page 13, lines 7-8; page 13, line 30 to page 14, line 3; page 19, lines 12-14; and page 30, lines 26-28. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Interview Summary

Applicants appreciate the courtesies that were extended by Examiner Le to Applicants' undersigned representative and to inventors Dr. Herman Staats and Dr. Soman Abraham during the telephone interview on March 2, 2009. Applicants concur that the Interview Summary mailed March 6, 2009 accurately reflects the substance of the telephonic interview.

Rejections Under 35 U.S.C. § 103

Claims 14, 16-19, and 28 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rosok *et al.* (U.S. Patent No. 4,834,976) in view of Lenney *et al.* (*J. Pharm. Sci. 66*:702 (1997)) as evidenced by Hood *et al.* (Immunology, 2nd Ed. (1984), pp. 371-73). (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner alleges that Rosok *et al.* teaches the administration of a composition comprising an immunogen and an antimicrobial agent with a pharmaceutical carrier. (Office Action, page 4). The Examiner is of the opinion that Rosok *et al.* used antibodies to *P. aeruginosa* as an antigen to induce an immune response for the treatment or prophylaxis of *P. aeruginosa* infection and that Rosok *et al.* suggested using the antibodies as an antigen. (Office Action, page 5). The Examiner further states that administration of the composition

of Rosok *et al.* would inherently induce an immune response, as evidenced by Hood *et al.* (Office Action, page 4). The Examiner further states that the immune response induced by the composition of Rosok *et al.* would necessarily include the production of anti-idiotype antibodies, which indicates a humoral immune response to provide treatment or prophylaxis. (Office Action, page 5).

Applicants respectfully disagree. The present invention is directed to methods of inducing an immune response (claim 14) or enhancing a protective immune response to an immunogen (claim 29), comprising concurrently administering an immunogen and compound 48/80 to a subject. In contrast, Rosok *et al.* does not teach administering an immunogen to induce an immune response. It is clear from reading Rosok *et al.* that the antibodies targeted to *P. aeruginosa* flagella were administered for the purposes of passive immunization, not for the induction of an immune response. In fact, Rosok *et al.* specifically states that mice were "passively immunized with antibodies" (column 18, lines 56-59; column 24, lines 63-66). Furthermore, analysis of the experimental data disclosed in Rosok *et al.* clearly shows that no *de novo* immune response was induced by the administration of the antibodies. Rosok *et al.* describes experiments using a burned mouse model in which antibodies were administered intravenously one to two hours prior to burn and challenge (Examples 4 and 8). Immediately after the burn the animals received a bacterial challenge. The data for each experiment (Tables I-V) showed that mice administered control antibodies started to die two days after challenge, while mice administered the matching anti-flagella antibody were protected as early as two days after challenge. These data demonstrate passive protection that is observed very quickly (*i.e.*, by 2 days) after passive transfer; in this time frame there is not enough time to induce a *de novo* protective immune response in the immunized individual. Moreover, the protective effect did not last in most of the studies as the protected mice started to die after a few days. If an active immune response had been induced, the protective effect would increase over time, not decrease. Thus, contrary to the Examiner's interpretation, Rosok *et al.* does not teach or suggest the induction of an immune response by administering antibodies as immunogens as no induced immune response was disclosed. Any protection observed in these experiments was passively derived from the administered antibodies themselves.

The Examiner states that administration of the composition of Rosok *et al.* would inherently induce an immune response, as evidenced by Hood *et al.* (Office Action, page 4). Applicants respectfully disagree that administration of an antibody necessarily induces an immune response. Hood *et al.* is a textbook published twenty years prior to the effective filing date of the present application and is therefore not representative of the knowledge of one of ordinary skill in the art at the time the application was filed. Hood *et al.* describes a theory of a network of related responses involving the generation of anti-idiotypic antibodies. Hood *et al.* provides no evidence that administration of antibodies to a subject always induces an active immune response and, even if a response was raised, that it would be effective for prophylaxis or treatment of infection.

Numerous therapeutic antibodies have been approved by the FDA for treatment of disease, including the monoclonal antibodies Abciximab, Adalimumab, Alemtuzumab, Basiliximab, Bevacizumab, Cetuximab, Daclizumab, Eculizumab, Efalizumab, 99mTc-Fanolesomab, Gemtuzumab, Ibritumomab tiuxetan, Infliximab, 111In-capromab, Imciromab, Muromonab-CD3, Natalizumab, Omalizumab, Palivizumab, Panitumumab, Ranibizumab, Gemtuzumab ozogamicin, Rituximab, Tositumomab, and Trastuzumab and the polyclonal antibodies Botulism Immune Globulin, Digoxin Immune Fab, Hepatitis B Immune Globulin, Lymphocyte Immune Globulin, Rabies Immune Globulin, Rho(D) Immune Globulin, and Tetanus Immune Globulin. None of these antibodies used in human medicine would be effective if the host raised an immune response against the passively transferred antibody. Host antibody response/allergy (typically IgE antibody) will inhibit the activity of these passively transferred antibodies and render them useless. Therefore, the composition of Rosok *et al.* would not be effective if it was immunogenic and induced a host immune response against the passively transferred antibody. It is noteworthy that even Rosok *et al.* acknowledges that host immune response to passively delivered antibodies may render transferred antibodies useless (column 2, lines 42-48).

Applicants acknowledge that antibodies may be used as immunogens in certain situations. However, when antibodies are used as immunogens to induce an immune response against a natural pathogen, for example as an idiotypic antibody, the antibody used

as the immunogen normally does not react with the native antigen. Instead, the antibody used as the immunogen mimics an antigen on the natural pathogen so as to raise antibodies that recognize the antigen. Rosok *et al.* teaches the use of antibodies that react with the natural pathogen and are themselves able to mediate protection against the specific disease. Thus, Rosok *et al.* is silent regarding the use of antibodies as immunogens.

Lenney *et al.* does not remedy the deficiencies in Rosok *et al.* Lenney *et al.* does not disclose the use of immunogens to induce an immune response or the ability of compound 48/80 to act as an adjuvant. The combination of Rosok *et al.* and Lenney *et al.* fails to teach every limitation of the presently claimed invention. Thus, the Examiner has not made a *prima facie* case of obviousness. In addition, neither of the references provide any suggestion or incentive to modify the compositions disclosed therein to contain an immunogen and compound 48/80 for use in the induction of an immune response as neither reference teaches an immunogen or the induction of an immune response.

It is respectfully requested that the rejection of claims 14, 16-19, and 28 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Accordingly, Applicant submits that the present application is in condition for allowance and the same is earnestly solicited. The Examiner is encouraged to telephone the undersigned at 919-854-1400 for resolution of any outstanding issues.

Respectfully submitted,

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CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on April 2, 2009.

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Marthenn Salazar